

Appendix B – Details of included studies

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Table B1. Detailed study characteristics

Study ID	Country	Duration (weeks)	Strategy or cross-over trial?	Early escape (EE) design? (week of EE)	Arms	Baseline characteristics of patients from study arms included in review							
						N	Prior MTX (%)	Prior DMARDs, including MTX (%)	Dose MTX in MTX arms (mg/wk)	Disease duration (yrs)	DAS28	HAQ-DI	SJC
Abatacept													
AVERT 2015 ¹	International	52	N	N	1.MTX + PBO 2.MTX + ABAT 125mg sc/wk Excluded from review: 3.ABAT 125mg sc/wk	235	0	NR	10-20	0.5	5.4	1.5	11
Iwahashi 2014 ²	Japan	24	N	N	1.MTX + ABAT ~10 mg/kg IV 0, 2, then Q4W 2.MTX + ABAT 125mg sc/wk (after IV load)	118	100	100	7.3	6.4	5.8	1.3	17
ASSET 2013 ³	Europe	17	N	N	1.MTX + PBO 2.MTX + ABAT ~10 mg/kg IV 0, 2, then Q4W	50	100	100	17.1	2.2	5.3	NR	10
Takeuchi 2013a ⁴	Japan	24	N	N	1.MTX + PBO 2.MTX + ABAT 10 mg/kg IV 0, 2, then Q4W Excluded from review: 3.MTX + ABAT 2 mg/kg IV 0, 2, then Q4W	127	100	100	7.2	7.3	6	1.4	17.1
Matsubara 2012 ⁵	Japan	24	N	N	1.MTX + ABAT ~10 mg/kg IV 0, 2, then Q4W 2.MTX + ABAT 125 mg sc/wk (after IV load)	118	100	100	7.3	6.4	5.8	1.3	17
ACQUIRE 2011 ⁶	International	26	N	N	1.MTX + ABAT ~10 mg/kg IV 0, 2, then Q4W 2.MTX + ABAT 125mg sc/wk (after IV load)	1457	100	100	16.4	7.6	6.2	1.7	20.1
Shim 2010 ⁷	Korea	24	N	N	1.MTX + PBO 2.MTX + ABAT ~10 mg/kg IV 0, 2, then Q4W	112	100	100	15 (min)	NR	NR	NR	NR
AGREE 2009 ⁸	International	52	N	N	1.MTX + PBO 2.MTX + ABAT ~10 mg/kg IV 0, 2, then Q4W	509	2	3	18.5	0.5	6.3	1.7	22.4
AIM 2006 ⁹	USA	52	N	N	1.MTX + PBO	652	100	100	16	8.6	6.8	1.7	21.6

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					2.MTX + ABAT ~10 mg/kg IV 0, 2, then Q4W								
Kremer 2005 ¹⁰	International	52	N	N	1.MTX + PBO 2.MTX + ABAT 10 mg/kg IV 0, 2, then Q4W Excluded from review: 3.MTX + ABAT 2 mg/kg IV 0, 2, then Q4W	234	100	100	15.4	9.3	5.5	1	21.6
Adalimumab													
RA-BEAM 2015 ¹¹	International	24	N	Y (16)	1.MTX + PBO 2.MTX + ADA 40 mg sc Q2W Excluded from review: 3.MTX + Baricitinib 4 mg po OD	818	100	100	NA	NR	NR	NR	NR
Weinblatt 2015 ¹²	International	24	N	Y (12)	1.MTX + PBO 2.MTX + ADA 40 mg sc Q2W Excluded from review: 3.MTX + Clazakizumab 25 mg sc Q4W 4.MTX + Clazakizumab 100 mg sc Q4W 5.MTX + Clazakizumab 200 mg sc Q4W 6.Clazakizumab 100 mg sc Q4W 7.Clazakizumab 200 mg sc Q4W	120	100	100	16.9	6.3	6.2	1.7	18.2
HOPEFUL-I 2014 ¹³	Japan	26	N	Y (12)	1.MTX + PBO 2.MTX + ADA 40 mg sc Q2W	334	0	48	6.4	0.3	6.6	1.2	16.9
OPERA 2014 ¹⁴	Denmark	13	Y	N	1.MTX + IA triamcinolone + PBO 2.MTX + IA triamcinolone + ADA 40 mg sc Q2W	180	0	0	18.3	0.2	5.6	NR	10.5
HITHARD 2013 ¹⁵	Germany	24	Y	N	1.scMTX + PBO 2.scMTX + ADA 40 mg sc Q2W	172	0	0	15	0.1	6.2	1.4	10.4
OPTIMA 2013 ¹⁶	International	26	N	N	1.MTX + PBO 2.MTX + ADA 40 mg sc Q2W	1032	0	10	20 (target)	0.4	6	1.6	18
AUGUST-II 2011 ¹⁷	NR	26	N	N	1.MTX + PBO 2.MTX + ADA 40 mg sc Q2W Excluded from review: 3.MTX + Atacicept 150 mg Q weekly (with load) 4.MTX + Atacicept 150 mg Q weekly (without load)	155	100	100	25 (max)	8.6	5.8	1.6	16.3
Chen 2011 ¹⁸	China	12	N	N	1.MTX + PBO 2.MTX + ADA 40 mg sc Q 2 weeks Excluded from review: 3.MTX + ADA 80 mg sc Q 2 weeks	24	100	100	10-20	NR	NR	NR	8.7
Chen 2009 ¹⁹	Taiwan	12	N	N	1.MTX + PBO 2.MTX + ADA 40 mg sc Q2W	47	100	100	10-15	6.7	6.4	1.7	22.5
GUEPARD 2009 ²⁰	France	12	Y	N	1.MTX 2.MTX + ADA 40 mg sc Q2W	65	0	NR	20 (max)	0.4	6.2	1.6	10.1

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Huang 2009 ²¹	China	12	N	N	1.MTX + PBO 2.MTX + ADA 40 mg sc Q 2 weeks Excluded from review: 3.MTX + ADA 80 mg sc Q 2 weeks	181	100	100	7.5 (min)	4.3	NR	1.4	11.7
Bejarano 2008 ²²	UK	56	N	N	1.MTX + PBO 2.MTX + ADA 40 mg sc Q2W	148	0	NR	15.8	0.7	5.9	1.3	9.9
Kim 2007 ²³	Korea	24	N	Y (18)	1.MTX + PBO 2.MTX + ADA 40 mg sc Q2W	128	100	NR	16.5	6.8	NR	1.4	12.5
PREMIER 2006 ²⁴	Australia, Europe, North America	104	N	N	1.MTX + PBO 2.MTX + ADA 40 mg sc Q2W Excluded from review: 3.ADA 40 mg sc Q2W + PBO	525	0	32	16.6	0.7	6.3	1.5	21.6
DE019 2004 ²⁵	USA and Canada	52	N	Y (16)	1.MTX + PBO 2.MTX + ADA 40 mg sc Q2W Excluded from review: 3.MTX + ADA 20 mg sc Q2W	407	100	100	16.7	11	NR	1.5	19.2
ARMADA 2003 ²⁶	USA and Canada	24	N	Y (16)	1.MTX + PBO 2.MTX + ADA 40 mg sc Q2W Excluded from review: 3.MTX + ADA 20 mg sc Q2W 4.MTX + ADA 80 mg sc Q2W	129	100	100	16.4	11.7	NR	1.6	17.1
Certolizumab													
C-EARLY 2015 ²⁷	International	52	N	N	1.MTX + PBO 2.MTX + CTZ 400 mg sc 0, 2, 4 wks then 200 mg Q2W	876	0	0	21.4	NR	6.8	1.7	NR
C-OPERA 2014 ²⁸	Japan	52	N	N	1.MTX 2.MTX + CTZ 400 mg sc 0, 2, 4 wks then 200 mg Q2W	316	0	NR	11.6	0.3	5.5	NR	NR
JRAPID 2014 ²⁹	Japan	24	N	Y (12)	1.MTX + PBO 2.MTX + CTZ 400 mg sc 0, 2, 4 wks then 200 mg Q2W Excluded from review: 3.MTX + CTZ 200 mg sc 0, 2, 4 wks then 100 mg Q2W 4.MTX + CTZ 400 mg sc 0, 2, 4 wks then 400 mg Q2W	159	100	100	7.4	5.7	6.3	1.1	17
Choy 2012 ³⁰	USA and Europe	24	N	N	1.MTX + CTZ 400 mg sc Q4W 2.MTX + PBO	243	100	100	16.8	9.6	6.2	1.4	22.5
Kang 2012 ³¹	Korea	24	N	Y (12)	1.MTX + PBO 2.MTX + CTZ 400 mg sc 0, 2, 4 wks then 200 mg Q2W	121	100	100	13.5	6.3	7.4	1.5	16.4
RAPID-II 2009 ³²	USA and Europe	24	N	Y (16)	1.MTX + PBO 2.MTX + CTZ 400 mg sc 0, 2, 4 wks then 200 mg Q2W Excluded from review:	373	100	100	12.4	5.9	NR	1.6	21

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					3.MTX + CTZ 400 mg sc 0, 2, 4 wks then 400 mg Q2W								
RAPID-I 2008 ³³	International	52	N	Y (16)	1.MTX + PBO 2.MTX + CTZ 400 mg sc 0, 2, 4 wks then 200 mg Q2W Excluded from review: 3.MTX + CTZ 400 mg sc 0, 2, 4 wks then 400 mg Q2W	592	100	100	13.5	6.1	6.9	1.7	21.5
Etanercept													
EMPIRE 2014 ³⁴	UK	52; 78 (safety)	N	N	1.MTX + PBO 2.MTN 50 mg sc Q weekly	110	0	0	25	0.6	4.1	1	NR
Takeuchi 2013b ³⁵	Japan	52	N	N	1.MTX + PBO 2.ETN 25 mg sc twice weekly + PBO Excluded from review: 3.ETN 10 mg sc twice weekly + PBO	358	64	100	6.5	3	5.8	1	13.9
Huang 2012 ³⁶	China	12	N	N	1.MTX + PBO 2.MTN 25 mg sc twice weekly	33	100	100	10-15	NR	NR	NR	11.2
ESCAPE 2010 ³⁷	Predominantly Eastern Europe	12	N	N	1.MTX + PBO 2.MTN 50 mg sc Q weekly Excluded from review: 3.MTN + AZD5672 20 mg po od 4.MTN + AZD5672 50 mg po od 5.MTN + AZD5672 100 mg po od 6.MTN + AZD5672 150 mg po od	140	100	100	13.3	6.2	6.7	1.5	11
COMET 2008 ³⁸	Europe, Latin America, Asia, Australia	52	N	N	1.MTX + PBO 2.MTN 50 mg sc Q weekly	528	0	21	18.2	0.8	6.5	1.7	NR
Marcora 2006 ³⁹	UK	24	N	N	1.MTN 2.ETN 25 mg sc twice weekly	26	0	0	7.5-20	0.5	5.9	1.5	NR
Lan 2004 ⁴⁰	Taiwan	12	N	N	1.MTX + PBO 2.MTN + ETN 25 mg sc twice weekly	58	100	100	12.5-20	NR	NR	1.1	13.8
TEMPO 2004 ⁴¹	Europe	52	N	N	1.MTN + PBO 2.MTN + ETN 25 mg sc twice weekly 3.ETN 25 mg sc twice weekly + PBO	682	43	NR	17	6.6	NR	1.7	22.6
ERA 2000 ⁴²	North America	52	N	N	1.MTN + PBO 2.ETN 25 mg sc twice weekly + PBO Excluded from review: 3.ETN 10 mg sc twice weekly + PBO	424	0	43	19	1	NR	NR	24
Weinblatt 1999 ⁴³	NR	24	N	N	1.MTN + PBO 2.MTN + ETN 25 mg sc twice weekly	89	100	100	18.7	13	NR	1.5	19
Golimumab													
GOBEFORE	International	52	N	Y (28)	1.MTN + PBO	318	0	51	19.1	3.2	6.2	1.5	15.4

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2013 ⁴⁴					2.MTX + GOL 50 mg sc Q monthly Excluded from review: 3.GOL 100 mg sc Q monthly + PBO 4.MTX + GOL 100 mg sc Q monthly								
GOFURTHER 2013 ⁴⁵	International	24	N	Y (16)	1.MTX + PBO 2.MTX + GOL 2 mg/kg IV 0, 4 then Q8W	592	100	100	15-25	6.9	6	1.6	14.9
NCT01248780 2013 ⁴⁶	China	24	N	Y (16)	1.MTX 2.MTX + GOL 50 mg sc Q monthly	264	100	100	7.5-20	NR	NR	NR	NR
GOFORTH 2012 ⁴⁷	Japan	24	N	Y (16)	1.MTX + PBO 2.MTX + GOL 50 mg sc Q monthly Excluded from review: 3.MTX + GOL 100 mg sc Q monthly	174	100	100	6-8	8.7	5.6	1	11.6
GOFORWARD 2009 ⁴⁸	International	24	N	Y (16)	1.MTX + PBO 2.MTX + GOL 50 mg sc Q monthly Excluded from review: 3.GOL 100 mg sc Q monthly + PBO 4.MTX + GOL 100 mg sc Q monthly	222	100	100	15	5.7	6.1	1.3	12.4
Kay 2008 ⁴⁹	International	16; 20 (safety)	N	N	1.MTX + PBO 2.MTX + GOL 50 mg sc Q monthly Excluded from review: 3.MTX + GOL 50 mg Q2W 4.MTX + GOL 100 mg sc Q monthly 5.MTX + GOL 100 mg Q2W	70	100	100	10 (min)	6.9	6.3	1.5	13.5
Infliximab													
MacIsaac 2014 ⁵⁰	Eastern Europe	14	N	N	1.MTX + PBO 2.MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	61	100	100	NA	NR	6.2	NR	NR
Kim 2013 ⁵¹	Korea	30	N	N	1.MTX + PBO 2.MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	138	100	100	12.5 (min)	8.6	NR	1.4	19.6
Li 2013 ⁵²	China	24	N	Y (16)	1.MTX 2.MTX + GOL 50 mg sc Q monthly	264	100	100	7.5-20	NR	NR	NR	NR
Tam 2012 ⁵³	Hong Kong	26	Y	N	1.MTX 2.MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	40	100	100	7.5-20	0.4	4.8	1.3	5
Xia 2011 ⁵⁴	China	30	N	N	1.MTX 2.MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	44	NR	NR	10 (target)	7.9	5.1	NR	NR
Durez 2007 ⁵⁵	Belgium	52	N	N	1.MTX 2.MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W Excluded from review: 3.MTX + IV methylprednisolone	29	0	NR	18.1	0.4	5.3	1.4	11.4
Abe 2006 ⁵⁶	Japan	14	N	N	1.MTX + PBO 2.MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W Excluded from review: 3.MTX + IFX 10 mg/kg IV 0, 2, 6 then Q8W	96	100	100	7.2	8.3	NR	NR	14.3
START 2006 ⁵⁷	International	22	N	N	1.MTX + PBO 2.MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	721	100	100	15	8.1	NR	1.5	15

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					Excluded from review: 3.MTX + IFX 10 mg/kg IV 0, 2, 6 then Q8W								
Zhang 2006 ⁵⁸	China	18	N	N	1.MTX + PBO 2.MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	173	100	100	7.5-20	7.6	NR	NR	NR
BEST 2005 ⁵⁹	Netherlands	13	Y	N	1.MTX (sequential monotherapy) 2.MTX (step-up combination) 3.MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W (initial IFX combination) Excluded from review: 4.MTX + SSZ 2g po od + Prednisone 60 mg po od (taper) (initial DMARD combo)	375	0	9	1.15 2.15 3.25	0.5	NR	1.4	NR
Quinn 2005 ⁶⁰	UK	54	N	N	1.MTX + PBO 2.MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	20	0	0	17	0.6	NR	1.3	NR
ASPIRE 2004 ⁶¹	International	54	N	N	1.MTX + PBO 2.MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W Excluded from review: 3.MTX + IFX 6 mg/kg IV 0, 2, 6 then Q8W	671	0	32	15.3	0.8	NR	1.5	21.4
ATTRACT 2000 ⁶²	North America, Europe	54	N	N	1.MTX + PBO 2.MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W Excluded from review: 3.MTX + IFX 3 mg/kg IV 0, 2, 6 then Q4W 4.MTX + IFX 10 mg/kg IV 0, 2, 6 then Q8W 5.MTX + IFX 10 mg/kg IV 0, 2, 6 then Q4W	174	100	100	15	10.5	NR	1.7	21.5
Rituximab													
IMAGE 2012 ⁶³	International	104	N	N	1.MTX + PBO 2.MTX + RTX 2 x 1000 mg IV 2 weeks apart Excluded from review: 3.MTX + RTX 2 x 500 mg IV 2 weeks apart	499	0	69	7.5-20	0.9	7	1.7	20.8
SERENE 2010 ⁶⁴	International	24	N	Y (16)	1.MTX + PBO 2.MTX + RTX 2 x 1000 mg IV 2 weeks apart Excluded from review: 3.MTX + RTX 2 x 500 mg IV 2 weeks apart	342	100	100	16.4	7	6.5	NR	20.2
DANCER 2006 ⁶⁵	International	24	N	N	1.MTX + PBO 2.MTX + RTX 2 x 1000 mg IV 2 weeks apart Excluded from review: 3.MTX + RTX 2 x 500 mg IV 2 weeks apart	341	100	100	15.2	10.1	6.7	1.7	21.6

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Edwards 2004 ⁶⁶	Australia, Canada, Israel, Europe	24	N	N	1.MTX + PBO 2.MTX + RTX 2 x 1000 mg IV 2 weeks apart Excluded from review: 3.RTX 2 x 1000 mg IV 2 weeks apart + PBO 4.RTX + Cyclophosphamide	80	100	100	10 (target)	11.5	6.8	1.9	21
Tocilizumab													
SURPRISE 2016 ⁶⁷	Japan	52	N	N	1.MTX + TCZ 8 mg/kg IV Q4W 2.TCZ 8 mg/kg IV Q4W	226	100	100	8.6	3.7	5.2	1.1	8.7
MEASURE 2015 ⁶⁸	North America, United Kingdom	24	N	Y (16)	1.MTX + PBO 2.MTX + TCZ 8 mg/kg IV Q4W	132	100	100	15	6.9	6.7	NR	NR
TOMERA 2014 ⁶⁹	Belgium	26	N	N	1.MTX + PBO 2.TCZ 8 mg/kg IV Q4W + PBO	30	0	0	15-20	0.8	4.5	1.1	6.4
ACT-RAY 2013 ⁷⁰	International	24	N	N	1.MTX + TCZ 8 mg/kg IV Q4W 2.TCZ 8 mg/kg IV Q4W + PBO	553	100	100	16	8.2	6.3	1.5	14.8
FUNCTION 2013 ⁷¹	International	52	N	Y (52)	1.MTX + PBO 2.MTX + TCZ 4 mg/kg IV Q4W 3.MTX + TCZ 8 mg/kg IV Q4W 4.TCZ 8 mg/kg IV Q4W	1157	0	NR	7.5-20	0.4	6.7	NR	NR
LITHE 2011 ⁷²	International	52	N	Y (16)	1.MTX + PBO 2.MTX + TCZ 4 mg/kg IV Q4W 3.MTX + TCZ 8 mg/kg IV Q4W	1190	100	100	15.1	9.2	6.5	1.5	17
AMBITION 2010 ⁷³	International	24	N	Y (NR)	1.MTX + PBO 2.TCZ 8 mg/kg IV Q4W + PBO	570	33	NR	15.5	6.3	6.8	1.6	19.1
SATORI 2009 ⁷⁴	Japan	24	N	N	1.MTX + PBO 2.MTX + TCZ 8 mg/kg IV Q4W	125	100	100	8 (target)	8.6	6.2	NR	12.6
OPTION 2008 ⁷⁵	International	24	N	Y (16)	1.MTX + PBO 2.MTX + TCZ 4 mg/kg IV Q4W 3.MTX + TCZ 8 mg/kg IV Q4W	622	100	100	14.7	7.6	6.8	1.6	20.1
CHARISMA 2006 ⁷⁶	Europe	16; 20 (safety)	N	N	1.MTX + PBO 2.MTX + TCZ 4 mg/kg IV Q4W 3.MTX + TCZ 8 mg/kg IV Q4W 6.TCZ 4 mg/kg IV Q4W 7.TCZ 8 mg/kg IV Q4W Excluded from review: 4.MTX + TCZ 2 mg/kg IV Q4W 5.TCZ 2 mg/kg IV Q4W	254	100	100	15.5	0.8	6.5	NR	11.4
Tofacitinib													
Conaghan 2014 ⁷⁷	International	52	N	N	1.MTX + PBO 2.MTX + TOFA 10 mg po BID Excluded from review:	73	0	NR	10-20	0.7	6.3	NR	NR

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					3.TOFA 10 mg po BID								
ORALSCAN 2013 ⁷⁸	International	24; 52 (safety)	N	Y (13)	1.MTX + PBO 2.MTX + TOFA 5 mg po BID Excluded from review: 3.MTX + TOFA 10 mg po BID	481	100	100	15-25	9	6.3	1.4	14.1
Kremer 2012 ⁷⁹	International	24	N	Y (12)	1.MTX + PBO 2.MTX + TOFA 5 mg po BID Excluded from review: 3.MTX + TOFA 1 mg po BID 4.MTX + TOFA 3 mg po BID 5.MTX + TOFA 10 mg po BID 6.MTX + TOFA 15 mg po BID 7.MTX + TOFA 20 mg po BID	140	100	100	16.5	9.1	5.2	1.3	14.9
Tanaka 2011 ⁸⁰	Japan	12	N	N	1.MTX + PBO 2.MTX + TOFA 5 mg po BID Excluded from review: 3.MTX + TOFA 1 mg po BID 4.MTX + TOFA 3 mg po BID 5.MTX + TOFA 10 mg po BID	55	100	100	8.4	8.4	5.9	1.2	14.7
Head to head biologics													
AMPLE 2014 ⁸¹	North and South America	104	N	N	1.MTX + ABAT 125 mg sc/wk (no IV load) 2.MTX + ADA 40 mg sc Q2W	646	100	100	17.4	1.8	5.5	1.5	15.9
ORALSTD 2012 ⁸²	International	26; 52 (safety)	N	Y (13)	1.MTX + PBO 2.MTX + ADA 40 mg sc Q2W 3.MTX + TOFA 5 mg po BID Excluded from review: 4.MTX + TOFA 10 mg po BID	501	100	100	7.5-25	7.9	6.5	1.5	16.6
ATTEST 2008 ⁸³	International	28	N	N	1.MTX + PBO 2.MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W 3.MTX + ABAT ~10 mg/kg IV 0, 2, then Q4W	431	100	100	16.4	7.8	6.8	1.8	20.6
Cuomo 2006 ⁸⁴	Italy	26	N	N	1.MTX + SSZ 2g/d 2.MTX + ADA 40 mg sc Q2W 3.MTX + ETN 25 mg sc twice weekly 4.MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	80	100	100	15 (target)	11.3	6.1	NR	NR
MTX + biologic therapy vs. MTX + DMARDs													
RACAT 2013 ⁸⁵	North America	24; 48 (safety)	Y	N	1.MTX + SSZ 2g/d + HCQ 400 mg/d + PBO 2.MTX + ETN 50 mg sc Q weekly + PBO	353	100	100	19.6	5.2	5.8	1.4	11.2
Joo 2012 ⁸⁶	Korea	16	N	N	1.MTX + LEF 10-20 mg/d 2.MTX + ETN 25 mg sc twice weekly	29	100	100	7.5-25	NR	NR	NR	NR

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SWEFOT 2012 ⁸⁷	Sweden	104	N	N	1.MTX + SSZ 2g/d + HCQ 400 mg/d 2.MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	245	100*	100	20 (target)	0.5	5.9	1.3	NR	
TEAR 2012 ⁸⁸	USA	102	N	N	1.MTX + ETN 50 mg sc Q weekly + PBO (Immediate treatment) 2.MTX + SSZ 2g/d + HCQ 400 mg/d + PBO (Immediate treatment) 3.MTX, then add ETN 50 mg sc Q weekly + PBO (Step-up treatment) 4.MTX, then add SSZ 2g/d + HCQ 400 mg/d + PBO (Step-up treatment)	755	21	24	20 (target)	0.3	5.8	1	12.8	
MTX+AZA														
Willkens 1992 ⁸⁹	USA and Canada	24	N	N	1.MTX + PBO 2.MTX + AZA 50-100 mg/d 3.AZA 50-150 mg/d + PBO	209	NR	100	1. 5-15 2. 5-7.5	8.6	NR	NR	17.3	
MTX+CyA														
CARDERA 2008 ⁹⁰	UK	104	N	N	1.MTX + PBO +/- Prednisolone 60 mg/d taper 2.MTX + CyA 3 mg/kg/d +/- Prednisolone 60 mg/d taper	467	NR	14	7.5-15	0.3	5.8	1.6	NR	
CIMESTRA 2006 ⁹¹	Denmark	52	N	N	1.MTX + IA betamethasone Q2-4W + PBO 2.MTX + IA betamethasone Q2-4W + CyA 2.5-4 mg/kg/d	160	0	0	13.8	3.5	5.4	1	11.5	
Sarzi-Puttini 2005 ⁹²	Italy	52	N	N	1.MTX + CyA 3-5 mg/kg/d 2.CyA 3-5 mg/kg/d Excluded from review: 3.CyA 3-5 mg/kg/d + HCQ 400 mg/d	67	0	0	12.5	1.2	NR	1.4	13	
Gerards 2003 ⁹³	Netherlands	48	N	Y (24)	1.MTX + CyA 2.5-5 mg/kg/d 2.CyA 2.5-5 mg/kg/d + PBO	120	0	14	13.7	0.2	NR	1.4	19	
Marchesoni 2003 ⁹⁴	Italy	52	N	N	1.IIM MTX 2.IIM MTX + CyA 3-4 mg/kg/d	61	0	0	10.4	0.9	5.1	1.3	13.6	
Giacomelli 2002 ⁹⁵	Italy	26	N	N	1.MTX + Prednisone 25 mg/d taper 2.MTX + Prednisone 25 mg/d taper + CyA 2.5-3.5 mg/kg/d	24	0	0	15	NR	NR	NR	15.3	
Machein 2002 ⁹⁶	Germany	26	N	N	1.IIM MTX + Prednisone 5 mg/d + PBO 2.IIM MTX + Prednisone 5 mg/d + CyA 2.5-3.5 mg/kg/d	13	100	100	15 (target)	0.9	5.9	NR	NR	
Kim 2000 ⁹⁷	Korea	16	N	N	1.MTX + PBO 2.MTX + CyA 2.5-4 mg/kg/d	40	100	100	15	8.2	NR	NR	11	
Tugwell 1995 ⁹⁸	USA and Canada	26	N	N	1.MTX + PBO 2.MTX + CyA 2.5-5 mg/kg/d	148	100	100	15 (max)	10.3	NR	1.4	16.2	
MTX+HCQ														
Singh 2012 ⁹⁹	India	16	N	N	1.MTX + HCQ (dosing NR) 2.LEF (dosing NR)	40	NR	NR	NA	NR	NR	NR	NR	

Appendix B – details of included studies

Shashikumar 2010 ¹⁰⁰	India	12	N	N	1.MTX + HCQ 200 mg/d 2.LEF 10 mg/d	60	NR	NR	7.5	NR	6.7	NR	9.6
Ghosh 2008 ¹⁰¹	India	26	N	N	1.MTX + HCQ 400 mg/d 2.SSZ 1.5g/d + HCQ 400 mg/d + PBO	110	0	0	10 (target)	0.3	6.8	NR	10.7
Mottaghi 2005 ¹⁰²	Iran	26 (safety)	N	N	1.MTX 2.MTX + CQ 150 mg/d	80	0	NR	7.5-12.5	NR	NR	NR	NR
Zhang 2004 ¹⁰³	China	52	N	N	1.MTX + LEF 20 mg/d 2.MTX + HCQ 400 mg/d	40	NR	NR	10-15	NR	NR	NR	19.5
Ferraz 1994 ¹⁰⁴	Brazil	26	N	N	1.MTX + PBO 2.MTX + CQ 250 mg/d	82	NR	100	7.5	7.7	NR	1.7	27.3
Trnavsky 1993 ¹⁰⁵	Czech Republic	26 (safety)	N	N	1.MTX + HCQ 200 mg/d 2.HCQ 200 mg/d + PBO	40	NR	NR	7.5	NR	NR	NR	8.2
MTX+IMGold													
METGO 2005 ¹⁰⁶	Canada	48	N	N	1.MTX + PBO 2.MTX + IM Gold 50 mg/wk	65	100	100	18.4	3.2	NR	1.4	11
MTX+LEF													
CareRA 2015 ¹⁰⁷	Belgium	16	Y	N	1.MTX + prednisone 2.MTX + LEF 10 mg/d + prednisone Excluded from review: 3.MTX + SSZ 2 g/d + prednisone	192	0	0	15	0.7	5.1	1	10.7
Mehrotra 2006 ¹⁰⁸	India	36; 156 (safety)	N	N	1.MTX 2.MTX + LEF 20 mg/d	466	NR	NR	1. 10-15 2. 10	NR	NR	NR	NR
Kremer 2002 ¹⁰⁹	USA and Canada	24	N	N	1.MTX + PBO 2.MTX + LEF 100 mg/d x 3, then 10-20 mg/d	263	100	100	16.4	11.6	NR	1.5	18
MTX+SSZ													
MASCOT 2007 ¹¹⁰	Scotland	76	N	N	1.MTX + PBO 2.MTX + SSZ 40 mg/kg/d 3.SSZ 40 mg/kg/d + PBO	165	0	100	13.7	1	NR	NR	NR
Tascioglu 2003 ¹¹¹	Turkey	52	N	N	1.MTX 2.MTX + SSZ 2 g/d	70	0	0	7.5	0.6	NR	1.1	10.7
Islam 2000 ¹¹²	Bangladesh	30	N	N	1.MTX 2.MTX + SSZ 2 g/d	54	NR	NR	7.5-15	0.2	NR	NR	16.7
Dougados 1999 ¹¹³	Finland, France, Germany	52	N	N	1.MTX + PBO 2.MTX + SSZ 2-3 g/d 3.SSZ 2-3 g/d + PBO	205	0	0	7.5-15	0.2	NR	1.3	9.8
Haagsma 1997 ¹¹⁴	Netherlands	52	N	N	1.MTX + PBO 2.MTX + SSZ 2-3 g/d 3.SSZ 2-3 g/d + PBO	105	0	0	7.5-15	0.2	NR	1	19.3
Haagsma 1994 ¹¹⁵	Netherlands	24	N	N	1.MTX 2.MTX + SSZ 2g/d	40	0	100	8.1	5	NR	NR	22.6
MTX+SSZ+HCQ													

Appendix B – details of included studies

tREACH 2013 ¹¹⁶	Netherlands	13	Y	N	1.MTX + Prednisone 15 mg/d taper 2.MTX + SSZ 2g/d + HCQ 400 mg/d + Prednisone 15 mg/d taper Excluded from review: 3.MTX + SSZ 2g/d + HCQ 400 mg/d + IM corticosteroid	190	0	0	25 (target)	0.5	4.8	1	9.5
Gubar 2008 ¹¹⁷	Russia	78	N	N	1.MTX 2.MTX + SSZ 2g/d + HCQ 200 mg/d	40	0	NR	7.5-17.5	2	NR	1.8	12.7
Odell 2002 ¹¹⁸	USA	104	N	N	1.MTX + HCQ 400 mg/d + PBO 2.MTX + SSZ 1-2 g/d + PBO 3.MTX + SSZ 1-2 g/d + HCQ 400 mg/d	171	54	NR	7.5-17.5	6.9	NR	NR	21.4
Odell 1996 ¹¹⁹	USA	104	N	N	1.MTX + PBO 2.MTX + SSZ 1g/d + HCQ 400 mg/d 3.SSZ 1g/d + HCQ 400 mg/d + PBO	102	11	100	7.5-17.5	8.6	NR	NR	29.8
Azathioprine													
Sigidin Ya 1994 ¹²⁰	Russia	52	N	N	1.MTX 2.AZA 2.5 mg/kg/d 3.CyA 2.5 mg/kg/d	60	NR	100	7.5	NR	NR	NR	9.5
Westedt 1994 ¹²¹	Netherlands	24	N	N	1.MTX 2.AZA 1-2 mg/kg/d	38	0	100	7.3	13.9	NR	NR	10.5
Jeurissen 1991 ¹²²	Netherlands	24	N	N	1.MTX + PBO 2.AZA 100-150 mg/d + PBO	64	0	100	8.8	11	NR	NR	18.7
Arnold 1990 ¹²³	Australia	24	N	N	1.MTX 2.AZA 100 mg/d	53	NR	100	10	13	NR	NR	NR
Hamdy 1987 ¹²⁴	Canada	24	N	N	1.MTX + PBO 2.AZA 100-150 mg/d	42	0	100	12	8.7	NR	NR	21.9
Cyclosporin													
Singh 2000 ¹²⁵	India	26	N	N	1.MTX 2.CyA 2.5-5 mg/kg/d	100	NR	100	15-30	5.5	NR	1.2	14
Drosos 1998 ¹²⁶	Greece	104	N	N	1.MTX + Prednisone 7.5 mg/d taper 2.CyA 3 mg/kg/d + Prednisone 7.5 mg/d taper	103	0	0	10	2.2	NR	NR	12.2
Hydroxychloroquine													
Alam 2012 ¹²⁷	Bangladesh	24	N	N	1.MTX 2.HCQ 200-400 mg/d	60	NR	NR	7.5-17.5	2.1	9.2	NR	NR
Van Jaarsveld 2000 ¹²⁸	Netherlands		Y	N	1.MTX 2.HCQ 400 mg/d 3.IM Gold 50 mg/wk Excluded from review: 4.NSAID	349	0	0	7.5-15	1	NR	1.3	NR
IM Gold													
Hamilton 2001 ¹²⁹	UK	48	N	N	1.MTX 2.IM Gold 50 mg/wk	141	0	NR	5-20	6	NR	2	NR

Appendix B – details of included studies

Rau 1997 ¹³⁰	Germany	52	N	N	1.1M MTX + PBO 2.1M Gold 50 mg/wk + PBO	174	0	11	7.5-15	2	NR	NR	15.2
Rau 1991 ¹³¹	Germany	52	N	N	1.1M MTX + PBO 2.1M Gold 50 mg/wk + PBO	99	0	NR	15	1.2	NR	NR	14
Morassut 1989 ¹³²	Canada	26	N	N	1.MTX + PBO 2.1M Gold 50 mg/wk + PBO	35	0	17	5-12.5	5	NR	NR	NR
Suarez-Almazor 1988 ¹³³	Canada	26	N	N	1.1M MTX + PBO 2.1M Gold 50 mg/wk + PBO	40	0	NR	10	4	NR	NR	13.9
Leflunomide													
Elmuntaser 2014 ¹³⁴	Libya	26	N	N	1.MTX 2.LEF 100 mg po weekly	40	NR	NR	10	NR	5.9	NR	NR
Fedorenko 2012 ¹³⁵	Russia	52	N	N	1.MTX 2.LEF 20 mg/d Excluded from review: 3.MTX + Prednisone 10 mg/d 4.MTX + Methylprednisolone 1g IV	72	NR	NR	20 (max)	0.5	6	NR	NR
Jaimes-Hernandez 2012 ¹³⁶	Mexico	52	N	Y (16)	1.MTX 2.LEF 100 mg po daily x 3, then 100 mg po Q weekly	85	1	4	10	1.9	5.7	0.9	8.2
Lisbona 2012 ¹³⁷	NR	16	N	N	1.MTX 2.LEF 20 mg/d	78	0	0	12.5-25	1	NR	NR	NR
Ishaq 2011 ¹³⁸	Pakistan	52	N	N	1.MTX + PBO 2.LEF 20 mg/d + PBO	240	NR	67	20	3.7	NR	1	16.5
Fiehn 2007 ¹³⁹	Germany	16	N	N	1.1M MTX + Prednisone 20 mg/d taper 2.LEF 100 mg/d x 3, then 20 mg/d + Prednisone 20 mg/d taper	40	0	NR	25	2.4	5.4	NR	NR
Bao 2003 ¹⁴⁰	China	12; 24 (safety)	N	N	1.MTX + PBO 2.LEF 20 mg/d + PBO	566	NR	NR	15	4.5	NR	NR	9.7
Lau 2002 ¹⁴¹	NR	16	N	N	1.MTX + PBO 2.LEF 20 mg/d + PBO	301	NR	NR	7.5-10	NR	NR	NR	NR
Reece 2002 ¹⁴²	Europe	17	N	N	1.MTX + PBO 2.LEF 100 mg/d x 3, then 20 mg/d + PBO	39	0	NR	7.5-15	4.7	NR	NR	NR
Shuai 2002 ¹⁴³	China	24	N	N	1.LEF 20 mg/d + PBO 2.MTX + PBO	80	NR	NR	15 (target)	4	NR	NR	9.8
Hu 2001 ¹⁴⁴	China	12	N	N	1.MTX + PBO 2.LEF 20 mg/d + PBO	81	NR	NR	15	3.4	NR	NR	NR
Lao 2001 ¹⁴⁵	China	24	N	N	1.MTX + PBO 2.LEF 20 mg/d + PBO	80	NR	NR	15 (target)	4.5	NR	NR	9.1
Bao 2000 ¹⁴⁶	China	24	N	N	1.MTX+PBO 2.LEF 20 mg/d + PBO	60	NR	NR	15 (target)	4.6	NR	NR	NR
Emery 2000 ¹⁴⁷	Europe and South Africa	52	N	N	1.MTX + PBO 2.LEF 100 mg/d x 3, then 20 mg/d + PBO	999	NR	67	12.6	3.7	NR	1	16.1
Kraan 2000 ¹⁴⁸	Netherlands	52	N	N	1.MTX + PBO 2.LEF 100 mg/d x 3, then 20 mg/d + PBO	15	NR	NR	7.5-15	6.6	NR	NR	15.5

Appendix B – details of included studies

ULTRA 1999 ¹⁴⁹	USA and Canada	52	N	Y (16)	1.MTX + PBO 2.LEF 100 mg/d x 3, then 20 mg/d + PBO 3.PBO	482	0	43	12	6.8	NR	0.8	13.7
Sulphasalazine													
Ferraccioli 2002 ¹⁵⁰	Italy	24	Y	N	1.MTX 2.CyA 3-5 mg/kg/d 3.SSZ 3g/d	126	0	100	10-20	1.4	NR	NR	9.3
Salaffi 1995 ¹⁵¹	Italy	24	N	N	1.IM MTX 2.SSZ 2g/d 3.HCQ 400 mg/d	85	NR	NR	10	6.6	NR	1.9	NR
sc vs. oral MTX													
Ahmed 2010 ¹⁵²	NR	24	N	N	1.MTX 2.scMTX	84	100	100	20-25	NR	NR	NR	NR
Braun 2008 ¹⁵³	Germany	24	N	Y (16)	1.MTX + PBO 2.scMTX + PBO	383	0	25	15	0.2	6.2	1.3	15
Placebo													
Pinheiro 1993 ¹⁵⁴	Brazil	12	N	N	1.MTX 2.PBO	36	0	69	7.5-12.5	8	NR	0.7	NR
Furst 1989 ¹⁵⁵	USA	18	N	Y (6)	1.MTX (3 dosing arms combined) 2.PBO	52	0	100	5-35	4.8	NR	NR	NR
Anderson 1985 ¹⁵⁶	USA	14; 27 (safety)	Y	N	1.IM MTX 2.PBO	12	0	100	5-25	14	NR	NR	NR
Weinblatt 1985 ¹⁵⁷	USA	12; 24 (safety)	Y	N	1.MTX 2.PBO	35	0	100	7.5-12.5	9.5	NR	NR	30.9
Williams 1985 ¹⁵⁸	USA	18	N	N	1.MTX 2.PBO	189	0	100	7.5-15	13.5	NR	NR	24

Trials are grouped by comparator and sorted chronologically. Trials may have more than one comparator, but are only listed once.

Abbreviations: ABAT, abatacept; ADA, adalimumab; AZA, azathioprine; CTZ, certolizumab; CQ, chloroquine; CyA, cyclosporine A; ETN, etanercept; HCQ, hydroxychloroquine; IFX, infliximab; IA, intra-articular; IM, intra-muscular; IV, intravenous; LEF, leflunomide; MTX, methotrexate; NR, not reported; PBO, placebo; RTX, rituximab; sc, subcutaneous; SSZ, sulphasalazine; TCZ, tocilizumab; TOFA, tofacitinib

* Patients in the SWEFOT study were naïve to DMARDs (including MTX) at baseline but had a 3-month run-in with MTX, after which only patients with an inadequate response were randomized.

Appendix B – details of included studies

Tables of individual study results for each analysis

Table B2. Individual study results for ACR50 response: MTX-naïve

Study ID	Arm	N	Events (ACR50 response)
AVERT 2015 ¹	MTX + PBO	116	54
	MTX + ABAT 125mg sc/wk	119	75
AGREE 2009 ⁸	MTX + PBO	253	107
	MTX + ABAT ~10 mg/kg IV 0, 2, then Q4W	256	147
HOPEFUL-I 2014 ¹³	MTX + PBO	163	63
	MTX + ADA 40 mg sc Q2W	171	110
HITHARD 2013 ¹⁵	scMTX + PBO	85	41
	scMTX + ADA 40 mg sc Q2W	87	56
OPTIMA 2013 ¹⁶	MTX + PBO	517	176
	MTX + ADA 40 mg sc Q2W	515	268
Bejarano 2008 ²²	MTX + PBO	73	33
	MTX + ADA 40 mg sc Q2W	75	42
PREMIER 2006 ²⁴	MTX + PBO	257	111
	MTX + ADA 40 mg sc Q2W	268	158
C-EARLY 2015 ²⁷	MTX + PBO	217	112
	MTX + CTZ 400 mg sc 0, 2, 4 wks then 200 mg Q2W	659	405
Takeuchi 2013b ³⁵	MTX + PBO	176	65
	ETN 25 mg sc twice weekly + PBO	182	113
COMET 2008 ³⁸	MTX + PBO	263	119
	MTX + ETN 50 mg sc Q weekly	265	181
TEMPO 2004 ⁴¹	MTX + PBO	228	98
	MTX + ETN 25 mg sc twice weekly	231	159
	ETN 25 mg sc twice weekly + PBO	223	107
ERA 2000 ⁴²	MTX + PBO	217	93
	ETN 25 mg sc twice weekly + PBO	207	101
GOBEFORE 2013 ⁴⁴	MTX + PBO	160	57
	MTX + GOL 50 mg sc Q monthly	158	67
Durez 2007 ⁵⁵	MTX	14	5
	MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	15	10
Quinn 2005 ⁶⁰	MTX + PBO	10	4
	MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	10	8
ASPIRE 2004 ⁶¹	MTX + PBO	298	88
	MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	373	160
IMAGE 2012 ⁶³	MTX + PBO	249	102
	MTX + RTX 2 x 1000 mg IV 2 weeks apart	250	156
FUNCTION 2013 ⁷¹	MTX + PBO	287	117
	MTX + TCZ 4 mg/kg IV Q4W	288	151
	MTX + TCZ 8 mg/kg IV Q4W	290	162
	TCZ 8 mg/kg IV Q4W	292	144
AMBITION 2010 ⁷³	MTX + PBO	284	95
	TCZ 8 mg/kg IV Q4W + PBO	286	126
Conaghan 2014 ⁷⁷	MTX + PBO	37	11
	MTX + TOFA 10 mg po BID	36	20
TEAR 2012 ⁸⁸	MTX + ETN 50 mg sc Q weekly + PBO (Immediate treatment)	244	91
	MTX + SSZ 2g/d + HCQ 400 mg/d + PBO (Immediate treatment)	132	41

Appendix B – details of included studies

CIMESTRA 2006 ⁹¹	MTX + IA betamethasone Q2-4W + PBO	80	42
	MTX + IA betamethasone Q2-4W + CyA 2.5-4 mg/kg/d	80	54
Sarzi-Puttini 2005 ⁹²	MTX + CyA 3-5 mg/kg/d	32	19
	CyA 3-5 mg/kg/d	35	6
Gerards 2003 ⁹³	MTX + CyA 2.5-5 mg/kg/d	60	29
	CyA 2.5-5 mg/kg/d + PBO	60	15
Marchesoni 2003 ⁹⁴	IM MTX	31	13
	IM MTX + CyA 3-4 mg/kg/d	30	15
MASCOT 2007 ¹¹⁰	MTX + PBO	54	4
	MTX + SSZ 40 mg/kg/d	56	6
	SSZ 40 mg/kg/d + PBO	55	3
Odell 2002 ¹¹⁸	MTX + HCQ 400 mg/d + PBO	25	10
	MTX + SSZ 1-2 g/d + PBO	24	11
	MTX + SSZ 1-2 g/d + HCQ 400 mg/d	30	20
Ferraccioli 2002 ¹⁵⁰	MTX	42	24
	CyA 3-5 mg/kg/d	42	13
	SSZ 3g/d	42	14
Braun 2008 ¹⁵³	MTX + PBO	190	110
	scMTX + PBO	193	117

Abbreviations: ABAT, abatacept; ADA, adalimumab; CyA, cyclosporine A; ETN, etanercept; HCQ, hydroxychloroquine; IFX, infliximab; IA, intra-articular; IM, intra-muscular; IV, intravenous; LEF, leflunomide; MTX, methotrexate; PBO, placebo; RTX, rituximab; sc, subcutaneous; SSZ, sulphasalazine; TCZ, tocilizumab

Appendix B – details of included studies

Table B3. Individual study results for radiographic progression: MTX-naïve

Study ID	Arm	N	Mean change	Standard error of the mean change
AGREE 2009 ⁸	MTX + PBO	242	1.06	0.16
	MTX + ABAT ~10 mg/kg IV 0, 2, then Q4W	242	0.63	0.11
HOPEFUL-I 2014 ¹³	MTX + PBO	128	2.4	0.28
	MTX + ADA 40 mg sc Q2W	148	1.5	0.5
PREMIER 2006 ²⁴	MTX + PBO	257	10.4	1.35
	MTX + ADA 40 mg sc Q2W	268	1.9	0.51
C-EARLY 2015 ²⁷	MTX + PBO	163	1.8	0.34
	MTX + CTZ 400 mg sc 0, 2, 4 wks then 200 mg Q2W	528	0.2	0.14
C-OPERA 2014 ²⁸	MTX	157	1.58	0.39
	MTX + CTZ 400 mg sc 0, 2, 4 wks then 200 mg Q2W	158	0.36	0.21
EMPIRE 2014 ³⁴	MTX + PBO	40	0.97	0.22
	MTX + ETN 50 mg sc Q weekly	30	0.84	0.27
Takeuchi 2013b ³⁵	MTX + PBO	171	9.82	1.16
	ETN 25 mg sc twice weekly + PBO	181	3.33	0.73
COMET 2008 ³⁸	MTX + PBO	230	2.44	0.51
	MTX + ETN 50 mg sc Q weekly	246	0.27	0.21
TEMPO 2004 ⁴¹	MTX + PBO	212	2.8	0.87
	MTX + ETN 25 mg sc twice weekly	218	-0.54	0.24
	ETN 25 mg sc twice weekly + PBO	212	0.52	0.32
ERA 2000 ⁴²	MTX + PBO	217	1.59	0.25
	ETN 25 mg sc twice weekly + PBO	207	1	0.26
GOBEFORE 2013 ⁴⁴	MTX + PBO	160	1.37	0.36
	MTX + GOL 50 mg sc Q monthly	159	0.74	0.42
ASPIRE 2004 ⁶¹	MTX + PBO	282	3.7	0.57
	MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	359	0.4	0.31
IMAGE 2012 ⁶³	MTX + PBO	229	1.95	0.37
	MTX + RTX 2 x 1000 mg IV 2 weeks apart	243	0.41	0.09
FUNCTION 2013 ⁷¹	MTX + PBO	267	1.14	0.26
	MTX + TCZ 4 mg/kg IV Q4W	267	0.42	0.18
	MTX + TCZ 8 mg/kg IV Q4W	273	0.08	0.13
	TCZ 8 mg/kg IV Q4W	275	0.26	0.11
Conaghan 2014 ⁷⁷	MTX + PBO	22	1.36	0.54
	MTX + TOFA 10 mg po BID	26	0.85	0.51
TEAR 2012 ⁸⁸	MTX + ETN 50 mg sc Q weekly + PBO (Immediate treatment)	105	0.6	0.41
	MTX + SSZ 2g/d + HCQ 400 mg/d + PBO (Immediate treatment)	45	2.7	1.88
CARDERA 2008 ⁹⁰	MTX + PBO +/- Prednisolone 60 mg/d taper	232	6.07	0.61
	MTX + CyA 3 mg/kg/d +/- Prednisolone 60 mg/d taper	235	3.77	0.51
CIMESTRA 2006 ⁹¹	MTX + IA betamethasone Q2-4W + PBO	80	1.12	0.37
	MTX + IA betamethasone Q2-4W + CyA 2.5-4 mg/kg/d	80	0.78	0.28

Appendix B – details of included studies

Table B4. Individual study results for withdrawals due to adverse events: MTX-naïve

Study ID	Arm	Exposure (pt-years)	Events (WDAE)
AVERT 2015 ¹	MTX + PBO	106	5
	MTX + ABAT 125mg sc/wk	111	5
AGREE 2009 ⁸	MTX + PBO	240	15
	MTX + ABAT ~10 mg/kg IV 0, 2, then Q4W	244	11
HOPEFUL-I 2014 ¹³	MTX + PBO	72.65	7
	MTX + ADA 40 mg sc Q2W	78.98	7
HITHARD 2013 ¹⁵	scMTX + PBO	36.46	4
	scMTX + ADA 40 mg sc Q2W	39	2
OPTIMA 2013 ¹⁶	MTX + PBO	244.25	17
	MTX + ADA 40 mg sc Q2W	245.25	27
Bejarano 2008 ²²	MTX + PBO	58.69	8
	MTX + ADA 40 mg sc Q2W	67.31	6
PREMIER 2006 ²⁴	MTX + PBO	429	20
	MTX + ADA 40 mg sc Q2W	482	33
EMPIRE 2014 ³⁴	MTX + PBO	80.99	0
	MTX + ETN 50 mg sc Q weekly	79.27	4
Takeuchi 2013b ³⁵	MTX + PBO	149.5	9
	ETN 25 mg sc twice weekly + PBO	166.5	19
COMET 2008 ³⁸	MTX + PBO	226	34
	MTX + ETN 50 mg sc Q weekly	243	29
TEMPO 2004 ⁴¹	MTX + PBO	193.5	33
	MTX + ETN 25 mg sc twice weekly	212	25
	ETN 25 mg sc twice weekly + PBO	196.5	26
ERA 2000 ⁴²	MTX + PBO	209.5	24
	ETN 25 mg sc twice weekly + PBO	200	12
GOBEFORE 2013 ⁴⁴	MTX + PBO	137.8	6
	MTX + GOL 50 mg sc Q monthly	327.3	31
Durez 2007 ⁵⁵	MTX	13	0
	MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	14.5	1
BEST 2005 ⁵⁹	MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W (initial IFX combination)	31.75	0
	MTX (sequential monotherapy)	61.25	1
Quinn 2005 ⁶⁰	MTX + PBO	10.38	0
	MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	9.87	1
ASPIRE 2004 ⁶¹	MTX + PBO	281.94	11
	MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	361.38	35
IMAGE 2012 ⁶³	MTX + PBO	422.11	15
	MTX + RTX 2 x 1000 mg IV 2 weeks apart	262.09	8
FUNCTION 2013 ⁷¹	MTX + PBO	256.5	18
	MTX + TCZ 4 mg/kg IV Q4W	259.5	29
	MTX + TCZ 8 mg/kg IV Q4W	258.5	49
	TCZ 8 mg/kg IV Q4W	264	32
AMBITION 2010 ⁷³	MTX + PBO	119.2	16
	TCZ 8 mg/kg IV Q4W + PBO	123.5	14
Conaghan 2014 ⁷⁷	MTX + PBO	32.5	5
	MTX + TOFA 10 mg po BID	28.5	4
TEAR 2012 ⁸⁸	MTX + ETN 50 mg sc Q weekly + PBO (Immediate treatment)	404.08	18
	MTX + SSZ 2g/d + HCQ 400 mg/d + PBO	209.88	12

Appendix B – details of included studies

	(Immediate treatment)		
Wilkens 1992 ⁸⁹	MTX + PBO	29.77	3
	MTX + AZA 50-100 mg/d	27.69	16
	AZA 50-150 mg/d + PBO	27.23	23
CARDERA 2008 ⁹⁰	MTX + PBO +/- Prednisolone 60 mg/d taper	361	58
	MTX + CyA 3 mg/kg/d +/- Prednisolone 60 mg/d taper	353	69
CIMESTRA 2006 ⁹¹	MTX + IA betamethasone Q2-4W + PBO	74	3
	MTX + IA betamethasone Q2-4W + CyA 2.5-4 mg/kg/d	74.5	1
Marchesoni 2003 ⁹⁴	IM MTX	30	2
	IM MTX + CyA 3-4 mg/kg/d	26	7
Ferraz 1994 ¹⁰⁴	MTX + PBO	18.75	1
	MTX + CQ 250 mg/d	18.75	3
MASCOT 2007 ¹¹⁰	MTX + PBO	67.23	14
	MTX + SSZ 40 mg/kg/d	69.42	12
	SSZ 40 mg/kg/d + PBO	70.15	10
Dougados 1999 ¹¹³	MTX + PBO	61.5	7
	MTX + SSZ 2-3 g/d	59.5	9
	SSZ 2-3 g/d + PBO	57.5	10
Haagsma 1997 ¹¹⁴	MTX + PBO	34	2
	MTX + SSZ 2-3 g/d	33	5
	SSZ 2-3 g/d + PBO	28	9
Haagsma 1994 ¹¹⁵	MTX	8.31	0
	MTX + SSZ 2g/d	9.69	2
tREACH 2013 ¹¹⁶	MTX + Prednisone 15 mg/d taper	23.38	3
	MTX + SSZ 2g/d + HCQ 400 mg/d + Prednisone 15 mg/d taper	22.75	0
Odell 2002 ¹¹⁸	MTX + HCQ 400 mg/d + PBO	94	5
	MTX + SSZ 1-2 g/d + PBO	84	5
	MTX + SSZ 1-2 g/d + HCQ 400 mg/d	103	4
Odell 1996 ¹¹⁹	MTX + PBO	48	7
	MTX + SSZ 1g/d + HCQ 400 mg/d	55	3
	SSZ 1g/d + HCQ 400 mg/d + PBO	49	3
Jeurissen 1991 ¹²²	MTX + PBO	14.08	0
	AZA 100-150 mg/d + PBO	12.23	13
Hamdy 1987 ¹²⁴	MTX + PBO	9	2
	AZA 100-150 mg/d	9.23	2
Braun 2008 ¹⁵³	MTX + PBO	81.9	10
	scMTX + PBO	82.2	18

Abbreviations: ABAT, abatacept; ADA, adalimumab; AZA, azathioprine; CTZ, certolizumab; CQ, chloroquine; CyA, cyclosporine A; ETN, etanercept; HCQ, hydroxychloroquine; IFX, infliximab; IA, intra-articular; IM, intra-muscular; IV, intravenous; LEF, leflunomide; MTX, methotrexate; PBO, placebo; RTX, rituximab; sc, subcutaneous; SSZ, sulphasalazine; TCZ, tocilizumab

Appendix B – details of included studies

Table B5. Individual study results for ACR50 response: MTX-inadequate response

Study ID	Arm	N	Events (ACR50 response)
Iwahashi 2014 ²	MTX + ABAT ~10 mg/kg IV 0, 2, then Q4W	59	37
	MTX + ABAT 125mg sc/wk (after IV load)	59	39
Takeuchi 2013a ⁴	MTX + PBO	66	4
	MTX + ABAT 10 mg/kg IV 0, 2, then Q4W	61	28
Matsubara 2012 ⁵	MTX + ABAT ~10 mg/kg IV 0, 2, then Q4W	59	37
	MTX + ABAT 125 mg sc/wk (after IV load)	59	39
ACQUIRE 2011 ⁶	MTX + ABAT ~10 mg/kg IV 0, 2, then Q4W	721	348
	MTX + ABAT 125mg sc/wk (after IV load)	736	368
Shim 2010 ⁷	MTX + PBO	57	9
	MTX + ABAT ~10 mg/kg IV 0, 2, then Q4W	55	18
AIM 2006 ⁹	MTX + PBO	219	39
	MTX + ABAT ~10 mg/kg IV 0, 2, then Q4W	433	205
Kremer 2005 ¹⁰	MTX + PBO	119	24
	MTX + ABAT 10 mg/kg IV 0, 2, then Q4W	115	48
RA-BEAM 2015 ¹¹	MTX + PBO	488	93
	MTX + ADA 40 mg sc Q2W	330	152
Weinblatt 2015 ¹²	MTX + PBO	61	10
	MTX + ADA 40 mg sc Q2W	59	28
AUGUST-II 2011 ¹⁷	MTX + PBO	76	11
	MTX + ADA 40 mg sc Q2W	79	30
Chen 2011 ¹⁸	MTX + PBO	8	2
	MTX + ADA 40 mg sc Q 2 weeks	16	11
Chen 2009 ¹⁹	MTX + PBO	12	2
	MTX + ADA 40 mg sc Q2W	35	12
Huang 2009 ²¹	MTX + PBO	60	9
	MTX + ADA 40 mg sc Q 2 weeks	121	39
Kim 2007 ²³	MTX + PBO	63	9
	MTX + ADA 40 mg sc Q2W	65	28
DE019 2004 ²⁵	MTX + PBO	200	19
	MTX + ADA 40 mg sc Q2W	207	86
ARMADA 2003 ²⁶	MTX + PBO	62	5
	MTX + ADA 40 mg sc Q2W	67	37
ESCAPE 2010 ³⁷	MTX + PBO	65	6
	MTX + ETN 50 mg sc Q weekly	75	35
Lan 2004 ⁴⁰	MTX + PBO	29	3
	MTX + ETN 25 mg sc twice weekly	29	19
Weinblatt 1999 ⁴³	MTX + PBO	30	1
	MTX + ETN 25 mg sc twice weekly	59	23
GOFURTHER 2013 ⁴⁵	MTX + PBO	197	26
	MTX + GOL 2 mg/kg IV 0, 4 then Q8W	395	138
GOFORTH 2012 ⁴⁷	MTX + PBO	88	13
	MTX + GOL 50 mg sc Q monthly	86	36
GOFORWARD 2009 ⁴⁸	MTX + PBO	133	18
	MTX + GOL 50 mg sc Q monthly	89	33
Kay 2008 ⁴⁹	MTX + PBO	35	2
	MTX + GOL 50 mg sc Q monthly	35	13
MacIsaac 2014 ⁵⁰	MTX + PBO	31	0
	MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	30	6
Abe 2006 ⁵⁶	MTX + PBO	47	4
	MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	49	15

Appendix B – details of included studies

START 2006 ⁵⁷	MTX + PBO	361	33
	MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	360	110
Zhang 2006 ⁵⁸	MTX + PBO	86	22
	MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	87	38
ATTRACT 2000 ⁶²	MTX + PBO	88	7
	MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	86	18
SERENE 2010 ⁶⁴	MTX + PBO	172	16
	MTX + RTX 2 x 1000 mg IV 2 weeks apart	170	44
DANCER 2006 ⁶⁵	MTX + PBO	122	16
	MTX + RTX 2 x 1000 mg IV 2 weeks apart	122	41
Edwards 2004 ⁶⁶	MTX + PBO	40	5
	MTX + RTX 2 x 1000 mg IV 2 weeks apart	40	17
MEASURE 2015 ⁶⁸	MTX + PBO	63	9
	MTX + TCZ 8 mg/kg IV Q4W	69	22
ACT-RAY 2013 ⁶⁹	MTX + TCZ 8 mg/kg IV Q4W	277	126
	TCZ 8 mg/kg IV Q4W + PBO	276	111
OPTION 2008 ⁷⁵	MTX + PBO	204	22
	MTX + TCZ 4 mg/kg IV Q4W	213	67
	MTX + TCZ 8 mg/kg IV Q4W	205	90
CHARISMA 2006 ⁷⁶	MTX + PBO	49	14
	MTX + TCZ 4 mg/kg IV Q4W	49	18
	MTX + TCZ 8 mg/kg IV Q4W	50	26
	TCZ 4 mg/kg IV Q4W	54	15
	TCZ 8 mg/kg IV Q4W	52	21
Kremer 2012 ⁷⁹	MTX + PBO	69	16
	MTX + TOFA 5 mg po BID	71	28
Tanaka 2011 ⁸⁰	MTX + PBO	28	4
	MTX + TOFA 5 mg po BID	27	22
AMPLE 2014 ⁸¹	MTX + ABAT 125 mg sc/wk (no IV load)	318	142
	MTX + ADA 40 mg sc Q2W	328	153
ORALSTD 2012 ⁸²	MTX + PBO	106	13
	MTX + ADA 40 mg sc Q2W	199	55
	MTX + TOFA 5 mg po BID	196	72
ATTEST 2008 ⁸³	MTX + PBO	110	22
	MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	165	61
	MTX + ABAT ~10 mg/kg IV 0, 2, then Q4W	156	63
RACAT 2013 ⁸⁵	MTX + SSZ 2g/d + HCQ 400 mg/d + PBO	178	41
	MTX + ETN 50 mg sc Q weekly + PBO	175	58
TEAR 2012 ⁸⁸	MTX, then add ETN 50 mg sc Q weekly + PBO (Step-up treatment)	255	83
	MTX, then add SSZ 2g/d + HCQ 400 mg/d + PBO (Step-up treatment)	124	46
METGO 2005 ¹⁰⁶	MTX + PBO	27	1
	MTX + IM Gold 50 mg/wk	38	10
Kremer 2002 ¹⁰⁹	MTX + PBO	133	8
	MTX + LEF 100 mg/d x 3, then 10-20 mg/d	130	34
Odell 2002 ¹¹⁸	MTX + HCQ 400 mg/d + PBO	33	13
	MTX + SSZ 1-2 g/d + PBO	31	5
	MTX + SSZ 1-2 g/d + HCQ 400 mg/d	28	12

Abbreviations: ABAT, abatacept; ADA, adalimumab; CTZ, certolizumab; CQ, chloroquine; CyA, cyclosporine A; ETN, etanercept; HCQ, hydroxychloroquine; IFX, infliximab; IA, intra-articular; IM, intra-muscular; IV, intravenous; LEF, leflunomide; MTX, methotrexate; NR, not reported; PBO, placebo; RTX, rituximab; sc, subcutaneous; SSZ, sulphasalazine; TCZ, tocilizumab

Appendix B – details of included studies

Table B6. Individual study results for radiographic progression: MTX-inadequate response

Study ID	Arm	N	Mean change	Standard error of the mean change
AIM 2006 ⁹	MTX + PBO	195	2.32	0.36
	MTX + ABAT ~10 mg/kg IV 0, 2, then Q4W	391	1.21	0.15
DE019 2004 ²⁵	MTX + PBO	172	2.7	0.52
	MTX + ADA 40 mg sc Q2W	183	0.1	0.35
GOFURTHER 2013 ⁴⁵	MTX + PBO	197	1.09	0.23
	MTX + GOL 2 mg/kg IV 0, 4 then Q8W	395	0.03	0.1
GOFORTH 2012 ⁴⁷	MTX + PBO	84	2.51	0.6
	MTX + GOL 50 mg sc Q monthly	81	1.05	0.41
GOFORWARD 2009 ⁴⁸	MTX + PBO	122	0.55	0.21
	MTX + GOL 50 mg sc Q monthly	86	0.6	0.3
ATTRACT 2000 ⁶²	MTX + PBO	64	7	1.29
	MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	71	1.3	0.71
AMPLE 2014 ⁸¹	MTX + ABAT 125 mg sc/wk (no IV load)	257	0.89	0.26
	MTX + ADA 40 mg sc Q2W	260	1.13	0.54
RACAT 2013 ⁸⁵	MTX + SSZ 2g/d + HCQ 400 mg/d + PBO	158	0.42	0.15
	MTX + ETN 50 mg sc Q weekly + PBO	160	0	0.29
SWEFOT 2012 ⁸⁷	MTX + SSZ 2g/d + HCQ 400 mg/d	109	7.23	1.22
	MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	106	4	0.98
TEAR 2012 ⁸⁸	MTX, then add ETN 50 mg sc Q weekly + PBO (Step-up treatment)	106	0.6	0.2
	MTX, then add SSZ 2g/d + HCQ 400 mg/d + PBO (Step-up treatment)	41	2.1	1

Abbreviations: ABAT, abatacept; ADA, adalimumab; ETN, etanercept; HCQ, hydroxychloroquine; IFX, infliximab; intravenous; LEF, leflunomide; MTX, methotrexate; PBO, placebo; RTX, rituximab; sc, subcutaneous; SSZ, sulphasalazine

Appendix B – details of included studies

Table B7. Individual study results for withdrawals due to adverse events: MTX-inadequate response

Study ID	Arm	Exposure (pt-years)	Events (WDAE)
Iwahashi 2014 ²	MTX + ABAT ~10 mg/kg IV 0, 2, then Q4W	26.54	3
	MTX + ABAT 125mg sc/wk (after IV load)	26.77	3
ASSET 2013 ³	MTX + PBO	7.52	0
	MTX + ABAT ~10 mg/kg IV 0, 2, then Q4W	8.66	0
Takeuchi 2013a ⁴	MTX + PBO	28.38	2
	MTX + ABAT 10 mg/kg IV 0, 2, then Q4W	28.15	0
Matsubara 2012 ⁵	MTX + ABAT ~10 mg/kg IV 0, 2, then Q4W	26.54	3
	MTX + ABAT 125 mg sc/wk (after IV load)	26.77	2
ACQUIRE 2011 ⁶	MTX + ABAT ~10 mg/kg IV 0, 2, then Q4W	349.25	26
	MTX + ABAT 125mg sc/wk (after IV load)	357.25	18
Shim 2010 ⁷	MTX + PBO	25.15	2
	MTX + ABAT ~10 mg/kg IV 0, 2, then Q4W	24.92	0
AIM 2006 ⁹	MTX + PBO	190.5	5
	MTX + ABAT ~10 mg/kg IV 0, 2, then Q4W	409	19
Kremer 2005 ¹⁰	MTX + PBO	95	11
	MTX + ABAT 10 mg/kg IV 0, 2, then Q4W	102.5	5
Weinblatt 2015 ¹²	MTX + PBO	24.92	0
	MTX + ADA 40 mg sc Q2W	26.08	1
AUGUST-II 2011 ¹⁷	MTX + PBO	35	2
	MTX + ADA 40 mg sc Q2W	37.75	2
Chen 2009 ¹⁹	MTX + PBO	2.77	0
	MTX + ADA 40 mg sc Q2W	7.73	3
Huang 2009 ²¹	MTX + PBO	13.73	1
	MTX + ADA 40 mg sc Q 2 weeks	27.69	2
Kim 2007 ²³	MTX + PBO	26	4
	MTX + ADA 40 mg sc Q2W	27.7	5
DE019 2004 ²⁵	MTX + PBO	161.3	13
	MTX + ADA 40 mg sc Q2W	179.2	28
ARMADA 2003 ²⁶	MTX + PBO	21	2
	MTX + ADA 40 mg sc Q2W	28.2	0
JRAPID 2014 ²⁹	MTX + PBO	25.16	2
	MTX + CTZ 400 mg sc 0, 2, 4 wks then 200 mg Q2W	36.8	3
Choy 2012 ³⁰	MTX + CTZ 400 mg sc Q4W	63.21	7
	MTX + PBO	56.58	6
RAPID-II 2009 ³²	MTX + PBO	40.8	2
	MTX + CTZ 400 mg sc 0, 2, 4 wks then 200 mg Q2W	100.7	12
RAPID-I 2008 ³³	MTX + PBO	91.4	4
	MTX + CTZ 400 mg sc 0, 2, 4 wks then 200 mg Q2W	303.3	19
ESCAPE	MTX + PBO	14.08	3

Appendix B – details of included studies

2010 ³⁷	MTX + ETN 50 mg sc Q weekly	16.38	5
Lan 2004 ⁴⁰	MTX + PBO	6.46	1
	MTX + ETN 25 mg sc twice weekly	6.46	1
Weinblatt 1999 ⁴³	MTX + PBO	12.46	1
	MTX + ETN 25 mg sc twice weekly	26.77	2
GOFURTHER 2013 ⁴⁵	MTX + PBO	79.18	3
	MTX + GOL 2 mg/kg IV 0, 4 then Q8W	190.54	9
GOFORTH 2012 ⁴⁷	MTX + PBO	35.08	1
	MTX + GOL 50 mg sc Q monthly	41.08	4
GOFORWARD 2009 ⁴⁸	MTX + PBO	51.35	5
	MTX + GOL 50 mg sc Q monthly	45.23	3
Kay 2008 ⁴⁹	MTX + PBO	11.9	3
	MTX + GOL 50 mg sc Q monthly	12.67	2
MacIsaac 2014 ⁵⁰	MTX + PBO	8.35	0
	MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	8.08	0
Abe 2006 ⁵⁶	MTX + PBO	11.98	1
	MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	12.86	1
START 2006 ⁵⁷	MTX + PBO	147.87	9
	MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	146.81	19
Zhang 2006 ⁵⁸	MTX + PBO	27.17	4
	MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	28.56	6
ATTRACT 2000 ⁶²	MTX + PBO	68.54	7
	MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	77.37	5
SERENE 2010 ⁶⁴	MTX + PBO	79.24	3
	MTX + RTX 2 x 1000 mg IV 2 weeks apart	81.36	3
DANCER 2006 ⁶⁵	MTX + PBO	56.77	0
	MTX + RTX 2 x 1000 mg IV 2 weeks apart	82.38	6
Edwards 2004 ⁶⁶	MTX + PBO	17.77	1
	MTX + RTX 2 x 1000 mg IV 2 weeks apart	18.23	1
MEASURE 2015 ⁶⁸	MTX + PBO	23.85	1
	MTX + TCZ 8 mg/kg IV Q4W	28.92	2
ACT-RAY 2013 ⁷⁰	MTX + TCZ 8 mg/kg IV Q4W	118.31	13
	TCZ 8 mg/kg IV Q4W + PBO	116.4	10
LITHE 2011 ⁷²	MTX + PBO	256.1	13
	MTX + TCZ 4 mg/kg IV Q4W	328.7	28
	MTX + TCZ 8 mg/kg IV Q4W	349.2	37
SATORI 2009 ⁷⁴	MTX + PBO	22.38	3
	MTX + TCZ 8 mg/kg IV Q4W	26.54	2
OPTION 2008 ⁷⁵	MTX + PBO	87.3	6
	MTX + TCZ 4 mg/kg IV Q4W	98.4	14
	MTX + TCZ 8 mg/kg IV Q4W	99.2	12

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CHARISMA 2006 ⁷⁶	MTX + PBO	17.12	4
	MTX + TCZ 4 mg/kg IV Q4W	17.5	6
	MTX + TCZ 8 mg/kg IV Q4W	17.88	6
	TCZ 4 mg/kg IV Q4W	18.65	6
	TCZ 8 mg/kg IV Q4W	18.46	5
ORALSCAN 2013 ⁷⁸	MTX + PBO	30.12	5
	MTX + TOFA 5 mg po BID	321.75	49
Kremer 2012 ⁷⁹	MTX + PBO	23.54	3
	MTX + TOFA 5 mg po BID	44.2	3
Tanaka 2011 ⁸⁰	MTX + PBO	5.88	2
	MTX + TOFA 5 mg po BID	5.77	4
AMPLE 2014 ⁸¹	MTX + ABAT 125 mg sc/wk (no IV load)	570	12
	MTX + ADA 40 mg sc Q2W	573	31
ORALSTD 2012 ⁸²	MTX + PBO	40.8	3
	MTX + ADA 40 mg sc Q2W	183	24
	MTX + TOFA 5 mg po BID	210.5	26
ATTEST 2008 ⁸³	MTX + PBO	58.42	1
	MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	85.35	9
	MTX + ABAT ~10 mg/kg IV 0, 2, then Q4W	81.58	3
RACAT 2013 ⁸⁵	MTX + SSZ 2g/d + HCQ 400 mg/d + PBO	152.8	13
	MTX + ETN 50 mg sc Q weekly + PBO	152.8	5
SWEPFOT 2012 ⁸⁷	MTX + SSZ 2g/d + HCQ 400 mg/d	199	22
	MTX + IFX 3 mg/kg IV 0, 2, 6 then Q8W	210	20
TEAR 2012 ⁸⁸	MTX, then add ETN 50 mg sc Q weekly + PBO (Step-up treatment)	428.6	17
	MTX, then add SSZ 2g/d + HCQ 400 mg/d + PBO (Step-up treatment)	201.06	7
Kim 2000 ⁹⁷	MTX + PBO	5.69	0
	MTX + CyA 2.5-4 mg/kg/d	5.69	3
Tugwell 1995 ⁹⁸	MTX + PBO	33.5	5
	MTX + CyA 2.5-5 mg/kg/d	32.75	11
METGO 2005 ¹⁰⁶	MTX + PBO	18.46	1
	MTX + IM Gold 50 mg/wk	30.92	4
Kremer 2002 ¹⁰⁹	MTX + PBO	53.77	9
	MTX + LEF 100 mg/d x 3, then 10-20 mg/d	53.08	16

Abbreviations: ABAT, abatacept; ADA, adalimumab; CTZ, certolizumab; CQ, chloroquine; CyA, cyclosporine A; ETN, etanercept; HCQ, hydroxychloroquine; IFX, infliximab; IA, intra-articular; IM, intra-muscular; IV, intravenous; LEF, leflunomide; MTX, methotrexate; NR, not reported; PBO, placebo; RTX, rituximab; sc, subcutaneous; SSZ, sulphasalazine; TCZ, tocilizumab; TOFA, tofacitinib

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